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Efficient synthesis of *p*-bis-(chlorodifluoromethyl)benzene

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Abstract

Selective, high yield partial fluorination of *p*-bis-(trichloromethyl)benzene to *p*-bis-(chlorodifluoromethyl)benzene has been accomplished by warming a slurry of the *p*-bis-(trichloromethyl)benzene in anhydrous HF which also contains a small quantity of inert solvent, such as 1,2-dichloroethane.

Keywords: Halex; AHF; Chlorine–fluorine exchange; Octafluoro[2.2]paracyclophane; AF4

1. Introduction

In developing a potential commercial process for the manufacture of 1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane (AF4), a major breakthrough was the discovery that *p*-bis-(chlorodifluoromethyl)benzene, **1**, could be converted to AF4 in yields up to 60% by treatment with Zn in dimethylacetamide at 100 °C, in a process that *did not require high dilution techniques* (Scheme 1) [1]. This process was able to be readily scaled up to prepare kilogram quantities of AF4.

Initially the immediate precursor, *p*-bis-(chlorodifluoromethyl)benzene, **1**, was prepared by the previously reported, straightforward two step method starting from terephthalaldehyde, via reaction with SF_4 to form the intermediate *p*-bis-(difluoromethyl)benzene, **2** [2], followed by photochemical chlorination of **2** to produce **1** (Scheme 2) [3].

However, although efficient and useful for preparing small quantities of **1** for research purposes, this procedure left much to be desired as a potential commercial source of large quantities of AF4 precursor **1**. First, the SF_4 reaction was a high pressure reaction, involving the use of a toxic gas, requiring an autoclave. Second, the relatively high cost of SF_4 would make the dichloride **1** prohibitively expensive. A more satisfactory source of dichloride **1** was required.

2. Results and discussion

Our first approach to devising a less expensive and readily scaleable source of the dichloride was to develop an alternative method for the preparation of the *p*-bis-(difluoromethyl)benzene, **2**, one that did not require SF_4 or an autoclave. This was able to be accomplished via a halex process, by simply heating *p*-bis-(dichloromethyl)-benzene, **3** [4,5], as a melt, for 8 h at 180 °C with a five-fold molar excess of CsF (Scheme 3), which provided **2** in a yield of 80%. KF could also be used for this reaction, but in that case a temperature of 280 °C and a time of 12 h were required to produce a yield of about 90%.

It is probable that the conversion of tetrachloride **3** to tetrafluoride **2** proceeds via direct, S_N2 nucleophilic displacement of chloride by fluoride. The success of this approach was quite surprising because the conventional approach to replacement of multiple benzylic chlorines by fluorines involves electrophilic catalysis (i.e., by SbF_3), via the formation of carbocation intermediates [6].

Nevertheless, although this new process averted the problems and expense of working with SF_4, the overall process of preparing the required symmetrical tetrachloride, **3**, combined with the relatively harsh conditions for the chlorine/fluorine exchange still made this a less than ideal process for scale-up and commercialization.

It was recognized from the outset that the ideal process, from both the point of view of expense and ease of commercialization, would be a process of simple, uncatalyzed chlorine/fluorine exchange of the inexpensive, commodity chemical,

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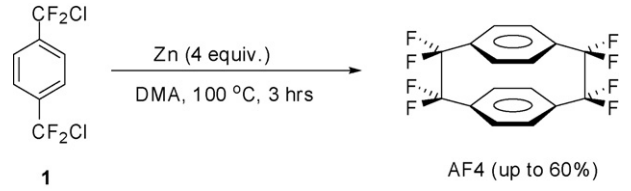
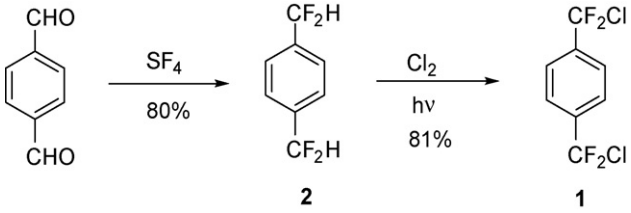
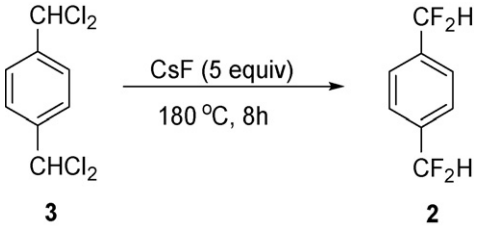


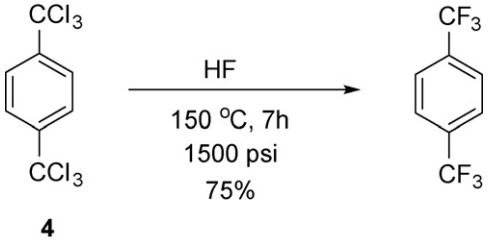
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

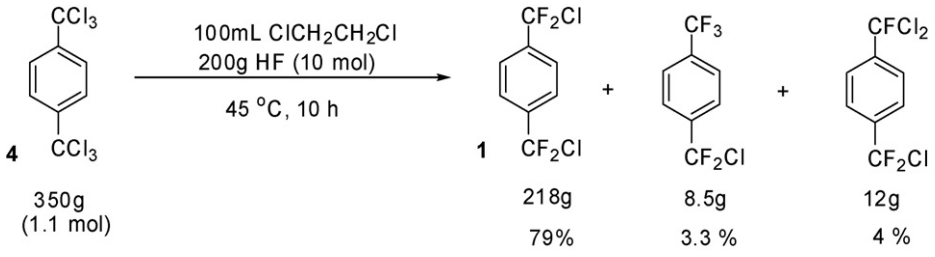
p-bis-(trichloromethyl)benzene, **4**, using anhydrous HF as the source of fluorine, and assuming that one could control the degree of fluorine incorporation in a satisfactory manner so as to obtain a reasonable selectivity in formation of the desired symmetrical tetrafluorodichloro compound **1**

The conversion of *p*-bis-(trichloromethyl)benzene, **4**, to *p*-bis-(trifluoromethyl)benzene by Cl/F exchange in anhydrous HF (AHF) is a well known process, exemplified by the conditions given below (Scheme 4) [7,8]. In spite of the considerable literature on this and related processes, there does not appear to be any significant published information related to attempts at partial fluorination of **4** that might allow preparation of the desired *p*-bis-(chlorodifluoromethyl)benzene **1**.

Initial attempts to control the extent of fluorination of the *p*-bis-(trichloromethyl)benzene using neat AHF and varying time and temperature, did not provide any encouraging results with respect to providing a reasonable selectivity for the desired dichloro tetrafluoro compound. It was only when a modest amount of an inert solvent, such as methylene chloride or 1,2-dichloroethane, was added, and the temperature maintained at about 45 °C for about 10 h, that it was found, quite amazingly, that the reaction could essentially be halted, with high conversion, at the symmetrical tetrafluoro stage, with very little over fluorination being observed (Scheme 5). The products could be readily separated by distillation, with the higher-boiling, under-fluorinated fraction being recycled in a subsequent reaction [9].

It was subsequently found that this process could be scaled up to pilot plant scale with the result that the *p*-bis-(chlorodifluoromethyl)benzene precursor **1** is now available at a reasonable price in whatever quantities required for the commercial preparation of AF4.

The selectivity observed for this process appears to be unique to the preparation of bis-(chlorodifluoromethyl)benzenes, since no similar selectivity was exhibited in the analogous reaction with (trichloromethyl)benzene [10–12]. Thus, the selectivity must derive from the effect of the *second* trihalomethyl group upon the relative ease of formation of the various carbocation intermediates involved in the specific chlorine/fluorine exchange processes. The presence of two trihalomethyl groups will slow down carbocation formation for each group, due to the electron withdrawing inductive effect of the second group. As the trihalomethyl groups accumulate fluorine, such inhibiting effect will increase. Slowing down fluorine/chlorine exchange has the potential to enhance any potential *selectivity* exhibited in the exchange process, and it must be surmised that once two chlorodifluoromethyl groups are present, at the given temperature, subsequent carbocation formation is sufficiently slowed down to allow the observed selectivity. The importance of the solvent in facilitating the observed selectivity must derive from its dissolving the *p*-bis-(trichloromethyl)benzene and thus providing a consistent liquid–liquid exchange process rather than a process of initial



Scheme 5.

solid–liquid exchange followed by increasing degrees of liquid–liquid exchange.

Neither the *ortho*- nor the *meta*-isomer of bis-(trichloromethyl)benzene has been examined under these conditions of chlorine/fluorine exchange, so it is not known whether they will exhibit similar selectivity with respect to formation of the respective bis-(chlorodifluoromethyl)benzene compounds.

3. Conclusion

In conclusion, a highly selective process for partial exchange of the benzylic chlorines of *p*-bis-(trichloromethyl)benzene to allow the high yield formation of AF4 precursor, *p*-bis-(chlorodifluoromethyl)benzene, is reported.

4. Experimental

4.1. General

NMR spectra were run using $CDCl_3$ as solvent, unless otherwise indicated. Proton, carbon and fluorine spectra were measured at 300, 75.46 and 282 MHz, respectively, using TMS as internal standard for ^1H and ^{13}C spectra and $CFCl_3$ for ^{19}F spectra. Coupling constants are reported in Hertz.

4.2. p-Bis-(difluoromethyl)benzene, 2

CsF (about 300 g) and *p*-bis-(dichloromethyl)benzene, **3** [4], (about 100 g) were added to a 500 mL three-necked flask. This mixture resulted in a molar ratio of CsF:**3** of about 4.8:1. The CsF and **3** were thoroughly mixed and heated to about 180 °C. At this temperature **3** melted and a slurry of **3** and CsF was formed. This slurry was maintained at about 180 °C and stirred for about 8 h. The liquid phase was then distilled from the flask at aspirator pressure (about 20 mmHg). Gas chromatographic analysis of the distillate was performed using a 10 ft SE-30 column, and the analysis indicated a clean conversion to product, with 58 g (80%) of *p*-bis-(difluoromethyl)benzene, **2**, being isolated.

2: bp 83–84 °C/30 mmHg [2]; ^1H NMR, δ 6.63 (t, $^2J_{FH} = 56$, 2H), 7.56 (s, 4H); ^{19}F NMR, δ −112.1 (d, $^2J_{FH} = 56.5$); ^{13}C NMR, δ 114.2 (t, $^1J_{CF} = 238$), 126.0 (t, $^3J_{CF} = 5.8$), 136.8 (t, $^2J_{CF} = 22.4$).

4.3. p-Bis-(chlorodifluoromethyl)benzene, 1

p-Bis-(trichloromethyl)benzene, **4**, (350 g, 1.1 mol) was placed into a 600 mL autoclave. To this was added 100 mL of 1,2-dichloroethane and 200 g (10 mol) anhydrous HF. The mixture was stirred at 45 °C for about 10 h, during which time the pressure rose to approximately 3 atm. Upon completion of the reaction, residual HF and HCl were removed by venting the mixture into 300 mL of 10% aqueous NaOH. The residual organic phase was then washed three times with 100 mL of 5% aqueous NaOH, and then three times with 300 mL of water. Subsequently, the organic phase was dried over $MgSO_4$, which was followed by simple distillation at reduced pressure to give three fractions:

- Fraction #1: (71–90 °C at ∼35 mmHg) yielded 27.5 g of material comprised of approximately 68 mol% **1** (19 g) with the remaining material (8.5 g) being largely chloropentafluoro product, as determined by ^{19}F NMR.
- Fraction #2: (90–95 °C at ∼35 mmHg) yielded 174 g of product comprised of 97% pure **1**.
- Fraction #3: (95–107 °C at ∼35 mmHg) yielded 37 g of material comprised of approximately 69 mol% (25 g) **1**, with the remaining material (12 g) being mainly comprised of trichloro trifluoro product, as determined by ^{19}F NMR.

The total yield of *p*-bis-(chlorodifluoromethyl)benzene, **1**, from the three fractions amounted to about 218 g (79%).

1: bp 59–60 °C/11 mmHg [13]; ^1H NMR, δ 7.73 (s); ^{19}F NMR, δ −50.4 (s); ^{13}C NMR, δ 125.3 (t, $^3J_{CF} = 4.9$), 125.7 (t, $^1J_{CF} = 308$), 139.2 (t, $^2J_{CF} = 26.9$).

Acknowledgement

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